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Biomimetic synthesis of the neolignans kadsurenone, denudatin B, *O*-methyl-liliflodione, and liliflol B

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Abstract

Synthesis of (±)-kadsurenone (**1**), (±)-denudatin B (**2**), (±)-*O*-methyl-liliflodione (**3a**), and (±)-liliflol B (**14**) is described. The key synthetic step is a biomimetic cationic cycloaddition between *E*- or *Z*-1,2-dimethoxy-4-propenylbenzene (**11**) and *ortho*-quinone monoketal **10**.

Kadsurenone (**1**) (from *Piper futokadsura*),[1] denudatin B (**2**) (from *Magnolia denudata*),[2] and liliflodione (**3**) (from *Magnolia liliflora*)[3] are members of a class of neolignans possessing hydrobenzofuran and bicyclo[3.2.1]octane skeletons. Kadsurenone has attracted the most attention due to its biological activity as a platelet-activating factor (PAF) antagonist.[1] The biosynthesis of these neolignans likely involves oxidative coupling between radical and/or cationic intermediates of propenyl- and allylphenols.[4] This guiding principal was first demonstrated by Büchi in his biomimetic synthesis of (±)-burchellin (**4**), (±)-2-epi, 3a-epiburchellin (**5**) and guianin (**6**) using *para*-quinone ketals and styrenes.[5] In this report, we describe a short synthesis of neolignans (±)-**1**–**3** resulting from a cationic cycloaddition between *ortho*-quinone monoketal **10** and propenylbenzene **11**.

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† Dedicated to the memory of Professor George Büchi, 1921–1998. Taken, in part, from Horne, D. A. Ph.D. Dissertation, 1988, Massachusetts Institute of Technology, Cambridge, MA.

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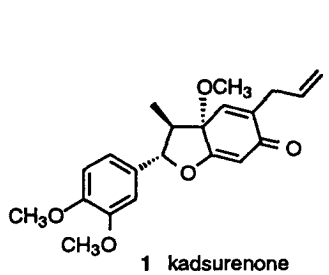
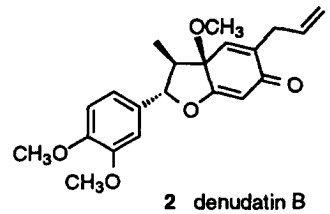
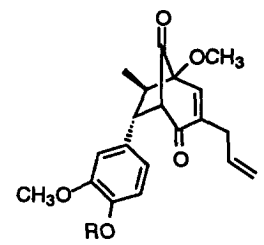


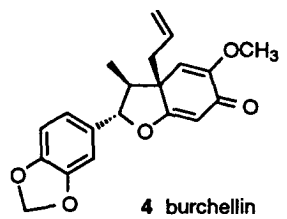
1 kadsurenone



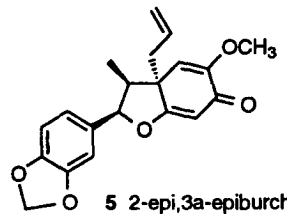
2 denudatin B



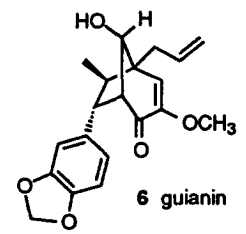
3 R = H
3a R = CH_3



4 burchellin

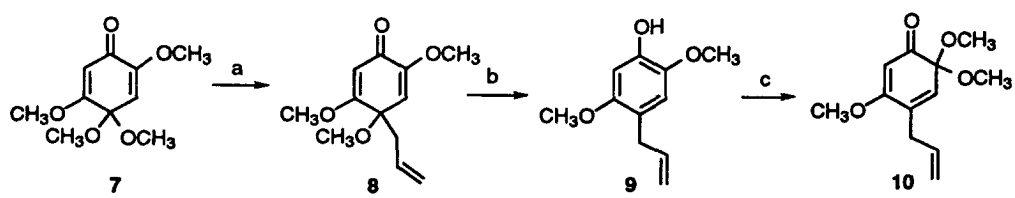


5 2-epi,3a-epiburchellin



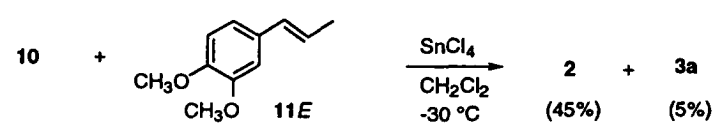
6 guianin

Comparison of the substituents surrounding the hydrobenzofuran skeleton of **1** and **2** (disregarding stereochemistry) with those of **4** and **5** reveals a transposition of the allyl and angular methoxyl appendages. This pointed to *o*-quinone ketal **10** as a potential cycloaddition precursor that would lead directly to the ring systems of **1–3** with the requisite substituents (Scheme 1). Regiospecific allylation of *p*-quinone ketal **7**[6] using allyltrimethylsilane and $TiCl_4$ proceeded efficiently to afford dienone **8**[7] in 92% yield. Reduction of **8** using zinc powder and dilute hydrochloric acid gave 5-methoxyeugenol **9** (from *Pentacalia andicola*).[8] This phenol has a pleasant clove-like aroma similar to eugenol (natural oil of cloves). Oxidation of phenol **9** with thallium trinitrate[9] in methanol gave *o*-quinone ketal **10**[10] as a light yellow oil (90%) along with dienone **8** (4%).



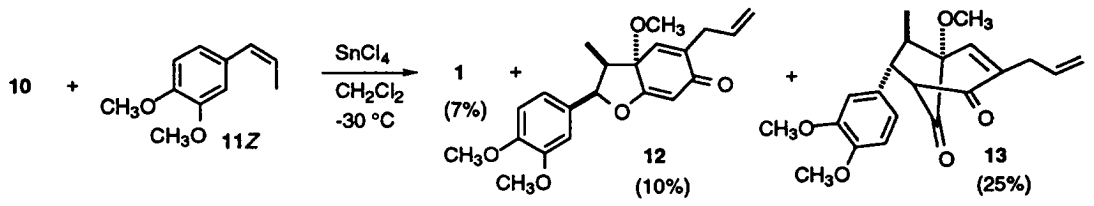
Scheme 1. (a) Allyltrimethylsilane, $TiCl_4$, –40°C, CH_2Cl_2, 92%. (b) Zn, HCl/THF 99%. (c) $Tl(ONO_2)_3 \cdot 3H_2O$, MeOH/$HC(OMe)_3$, K_2CO_3, rt, 90%

When ketal **10** and *E*-1,2-dimethoxy-4-propenylbenzene (**11**) were exposed to stannic chloride, a 45% yield of (±)-**2** along with 5% of **3a**[3] was obtained (Scheme 2).[11] NMR, UV, IR and MS data of synthetic **2** and **3a** were in complete agreement with spectroscopic data reported for the natural material. Several unsuccessful attempts using $BF_3 \cdot OEt_2$, $TiCl_4$, $MeSO_3H$, and HCl were made to increase the yield of the hydrobenzofuran product by varying the reaction conditions. Generally, when the cycloaddition was initiated with protic acids the overall yield was lower.



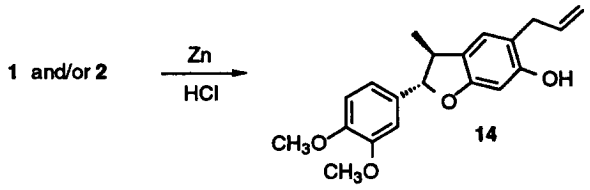
Scheme 2.

Treatment of ketal **10** and **11Z** with 2.5 equiv. of $SnCl_4$ (–30°C, CH_2Cl_2, 15 min) produced (±)-kadsurenone (**1**) (5%), (±)-7-epi-kadsurenone (**12**)[12] (7%), (±)-bicyclooctanone **13** (22%), and minor amounts of (±)-**2** (<2%) (Scheme 3). NMR, UV, IR, and MS data of synthetic **1** were in complete agreement with spectroscopic data reported for the natural material.



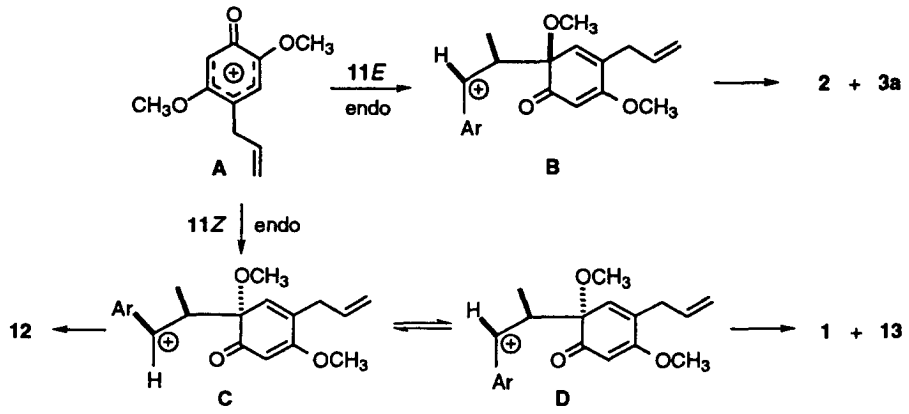
Scheme 3.

Both **2** and **3a** were stable under the conditions used for their generation. At 25°C, however, hydrobenzofuran **2** underwent irreversible isomerization to bicyclooctanone **3a** in methylene chloride containing $SnCl_4$.[13] Under analogous conditions, negligible isomerization of **1** after 30 min was detected at –30°C, although irreversible transformation to initially **12** then **13** was observed at rt after 5 h. Attempts to isomerize bicyclooctanones **3a** and **13** to hydrobenzofurans **1**, **2**, and **12** were unsuccessful. Reduction of **1** and **2** (Zn, 20 equiv., dil. HCl, THF, 25°C) gave racemic liliflol B (**14**)[3] (90%) (Scheme 4). Kadsurenone (**1**) has been synthesized by three other groups all of which utilized liliflol B (**14**) as the penultimate precursor in a low yielding oxidative methoxylation event.[11b–e,14]



Scheme 4.

To account for the formation of products, we assume that the reactions are initiated by cycloaddition of cationic intermediate **A** with olefin **11***E* or *-Z* wherein the aryl group adopts an *endo* orientation in the transition state leading to intermediates **B–D**. Upon C–O ring closure, **B** and **C** would give denudatin B (**2**) and 7-epi-kadsurenone (**12**), respectively. Kadsurenone (**1**) is believed to be derived from intermediate **D** which is the rotational isomer of **C**. Similarly, intermediates **B** and **D** lead to the formation of bicyclooctanones **3a** and **13**, respectively, via C–C bond formation. Finally, attempts to utilize *p*-quinol ether **8** in the cycloaddition process with **11** produced hydrobenzofuran and bicyclooctanone products;[15] however, the yields were poor in comparison to the analogous reaction with *p*-quinone ketal **10**.[16]



Since the initial reports of Büchi, a number of related studies[17] have appeared describing similar cycloaddition processes involving dienylcarbocations and styrenes, but none have directly produced the angular or bridgehead methoxy and allyl substituents found in the hydrobenzofuran series of denudatin B and kadsurenone or the bicyclooctane structure of liliflodione. The use of an *ortho*-quinone ketal in the present study serves as a novel and useful synthon for pentadienylcations leading to such systems.

Acknowledgements

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7. All new compounds gave satisfactory spectral analysis. Compound **8**: colorless solid, mp 136–137°C. ^{1}H NMR ($CDCl_3$): δ 2.62 (m, 2H), 3.12 (s, 3H), 3.71 (s, 3H), 3.80 (s, 3H), 5.06 (m, 2H), 5.32 (s, 1H), 5.58 (m, 1H), 5.70 (s, 1H); anal. calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19; found: C, 64.06; H, 7.21.
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10. Compound **10**: ^{1}H NMR ($CDCl_3$): δ 3.10 (d, *J*=5.5 Hz, 2H), 3.40 (s, 6H), 3.81 (s, 3H), 5.16 (m, 2H), 5.43 (s, 1H), 5.89 (m, 1H), 6.18 (t, *J*=1.5 Hz, 1H).
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12. Compound **12**: ^{1}H NMR ($CDCl_3$): δ 0.49 (d, *J*=7.2 Hz, 3H), 2.68 (m, 1H), 3.15 (m, 2H), 3.17 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 5.12 (m, 2H), 5.18 (m, 1H), 5.93 (s, 1H), 6.11 (d, *J*=5.3 Hz, 1H), 6.26 (t, *J*=1.9 Hz, 1H), 6.74 (d, *J*=2.2 Hz, 2H),

6.80 (dd, J=7.7, 2.0 Hz, 1H). **13**: ^{1}H NMR ($CDCl_3$): δ 1.07 (d, J=6.0 Hz, 3H), 2.47 (m, 2H), 3.12 (m, 2H), 3.52 (s, 1H), 3.64 (s, 3H), 3.85 (s, 6H), 5.19 (m, 2H), 5.87 (m, 1H), 6.59 (d, J=2.7 Hz, 1H), 6.66 (dd, J=8.8, 2.7 Hz, 1H), 6.79 (d, J=8.8 Hz, 1H), 7.05 (s, 1H).

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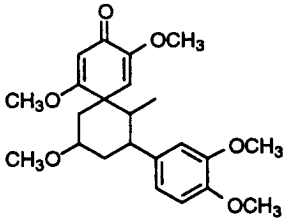
15. A related approach using *p*-quinol model compounds has been reported: Mortlock, S. V.; Seckington, J. K.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2305.
16. The major product (40–50%) resulting from the acid-facilitated reaction of *p*-quinol ether **8** and propenylbenzene **11*E*** has been tentatively assigned the spiro-dienone (futoenone-like) structure shown below as a mixture of diastereomers. This is a result of olefin addition γ to the carbonyl which is the site of initial ionization in **8**. In the case of *o*-quinone ketal **10** which affords significantly higher yields of hydrobenzofuran and bicyclooctanone products, initial ionization takes place α to the carbonyl (the requisite site of olefin addition).



17. See Ref. 11e and references cited therein.